

Main Pancreatic Duct Dilatation: a Sign of High Risk for Pancreatic Cancer

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Background: The prognosis of pancreatic ductal adenocarcinoma remains very poor, but is better in patients with a small tumor without local infiltration. The identification of the sign of high risk for pancreatic cancer will lead to early detection and improvement of the prognosis of this disease. The purpose of this study was to evaluate the main pancreatic duct dilatation as a sign of high risk for pancreatic cancer.

Methods: The diameter of the main pancreatic duct was measured by ultrasonography. The proportion of cases with main pancreatic duct dilatation was retrospectively examined in a pre-cancer group (39 subjects in whom pancreatic cancer developed more than 1 year later and surgically resected) and in a control group (10 244 subjects). Then the proportions in both groups were compared using the odds ratio.

Results: The proportion of cases with a slight dilatation (≥ 2 mm in diameter) of the main pancreatic duct was 65% in the pre-cancer group, more than 4 years before the resection of the pancreatic cancer. In contrast, it was 5.35% in the age-matched control subjects. The odds ratio of 32.5 (95% confidence interval: 10.9–107.3) shows a significant association between the main pancreatic duct dilatation and the pre-cancer condition. Moreover, the proportion and the mean diameter of the dilated duct in the pre-cancer group increased with time.

Conclusion: Slight dilatation of the main pancreatic duct appears to be a sign of high risk for pancreatic cancer. The systematic examination of high-risk subjects is recommended for the early detection of pancreatic cancer.

Key words: pancreatic cancer – main pancreatic duct dilatation – ultrasonography – risk factor

INTRODUCTION

Most cases of pancreatic ductal adenocarcinoma are unresectable when detected and the prognosis of this disease is very poor even after surgical resection (1–3). However, a recent study reported a better prognosis with a 61.0% 5-year survival rate in cases with a small tumor without local infiltration to adjacent soft tissue (3). If a risk factor or a preceding sign heralding pancreatic cancer could be identified and systematic examination performed on high-risk patients, as has been successfully undertaken in HBV- and HCV-positive subjects to screen for hepatocellular carcinoma (4), the prognosis of this disease could be markedly improved.

Clinically, we have sometimes encountered pancreatic cancer cases in which a slight dilatation of the main pancreatic duct had been indicated by ultrasonography several years prior to detection of the pancreatic cancer (5). In the present study, ultrasonograms of the pancreas obtained more than 1 year before surgical resection of pancreatic cancer were retrospectively examined to evaluate main pancreatic duct dilatation as a pre-sign of pancreatic ductal adenocarcinoma.

SUBJECTS AND METHODS

ULTRASONOGRAPHIC EXAMINATION

Routine upper abdominal ultrasonography was performed, taking about 15 min using conventional real-time sonographic equipment. The equipment used for this study were Models EUB-22, -20Z and -24F (Hitachi, Tokyo), SSD-250 (Aloka, Tokyo), EUB-25, -27 and -40 (Hitachi), SAL-35A and -270A (Toshiba, Tokyo), RT-3000 (Yokogawa, Tokyo), EUB-340,

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Table 1. Main pancreatic duct dilatation in control group, according to age ranges: No. of cases (%)

		Age range (mean) (years)			
<25 (21.7)	26–50 (42.9)	51–75 (63.0)	≥76 (79.7)	All ages (59.4)	
127	2219	7146	752	10 244	
<i>≥3 mm dilatation</i>					
0 (0.00)	11 (0.50)	89 (1.25)	24 (3.19)	124 (1.21)	
<i>≥2 mm dilatation</i>					
1 (0.79)	54 (2.44)	382 (5.35)	78 (10.37)	515 (5.03)	

-410 and -450 (Hitachi) and UM-9 and HDI-3000 (ATL, Bothell, WA). For each examination, about 10–20 images of the liver, spleen, pancreas, gall bladder, extra-hepatic bile duct and bilateral kidneys were recorded even if the request was limited to one organ. All images were filed and stored on instant film, thermal film or, in recent years, magnetic-optical discs. The diameter of the main pancreatic duct was measured at the body on the longitudinal view of the pancreas, between the upper edge of the anterior line and the posterior line of the main pancreatic duct. The diameter was graded into three ranks: <2, 2–3 and ≥3 mm. These findings were stored in a personal computer.

CONTROL GROUP

In 1997, upper abdominal ultrasonography was performed on 10 610 patients for the screening of abdominal disorders in our hospital. We excluded 366 subjects in whom some focal region was suspected to exist in the pancreatic area (264), the pancreatic body could not be visualized (100) or the regional cancer registry subsequently pointed out pancreatic cancer by the end of 1999 (2). The remaining 10 244 subjects were selected as the control group. They consisted of 5780 males and 4464 females, aged 13–93 years (mean 59.4 years).

PRE-CANCER GROUP

Between 1982 and 1997, 197 ordinary invasive pancreatic ductal adenocarcinomas were surgically resected and histologically confirmed in our hospital. No intraductal cancer was included. In 39 of them, upper abdominal ultrasonography was performed more than one year before the surgical resection of pancreatic cancer. These 39 patients were classified as the pre-cancer group. They consisted of 33 males and six females, ranging in age from 51 to 75 years (mean 64.5 years) at the time of surgery. Pancreaticoduodenectomy was performed on 17 patients, distal pancreatectomy on 15, segmental pancreatectomy of the body (6) on four and total pancreatectomy on three. The size of the resected cancer was <2 cm in 23 cases, 2–4 cm in nine, 4–6 cm in two and >6 cm in five.

Ultrasonographic examinations were performed 1–13 times (mean 3.2 times) on each subject during the 13–152-month period before surgery. The purpose or the symptom prompting the first abdominal ultrasonography was a medical checkup in 10 patients, ruling out hepatocellular carcinoma in chronic

viral hepatitis in 10, ruling out liver metastasis from other organs in nine, upper abdominal discomfort in four, bloody stool in two, preoperative work-up for cardiovascular surgery in two, lumbago in one and hematuria in one. No patient had a history of pancreatitis at the time of the first ultrasonography. When any abnormal findings in the pancreas were detected by ultrasonography, additional examinations such as X-ray CT and/or MRI and sometimes endoscopic retrograde pancreatography with pancreatic juice cytology were performed and pancreatic cancer was excluded.

Ultrasonograms of these cases were classified into three groups according to the period until surgical resection. There were 17 subjects in whom ultrasonography was performed at more than 4 years before surgery and 28 at more than 2 years. Within a month before surgery, ultrasonography was performed again on all 39 subjects. In cases in whom ultrasonography was performed more than once in a given period, the most recent finding was employed.

The proportion of cases with main pancreatic duct dilatation was determined in the pre-cancer group, according to the period until surgical resection. The incidence in the control group was also examined according to the age range. The proportions of the dilated cases in each group were compared using the odds ratio. Informed consent was obtained from all patients for statistical analysis of their clinical data including ultrasonography.

RESULTS

CONTROL GROUP

The proportions of the dilated cases in each age group are shown in Table 1. More than 3 mm dilatation was observed in 1.21% and more than 2 mm dilatation was observed in 5.03% of the subjects of all ages. The proportions were higher in the older age range. In the same age range as the pre-cancer group (51–75 years), these findings were observed in 1.25 and 5.35%, respectively.

PRE-CANCER GROUP

The proportions of the dilated cases in each period are shown in Table 2. More than 4 years before resection of the pancreatic cancer, main pancreatic duct dilatation of >3 mm was observed in 35.3% of 17 examined cases. However, it was observed in

Table 2. Main pancreatic duct dilatation in the pre-cancer group: No. of cases (%)

	Period until surgical resection			
	≥4 years	≥2 years	≥1 year	>1 month
No. of cases examined	17	28	39	39
<i>MPD* dilatation</i>				
≥3 mm	6 (35.3)	12 (46.2)	20 (51.3)	32 (82.1)
≥2 mm	11 (64.7)	19 (67.9)	32 (82.1)	33 (84.6)
Mean diameter of MPD* in the dilated cases (mm)	3.0	3.5	3.8	4.5

*MPD: main pancreatic duct.

Table 3. Main pancreatic duct dilatation in the pre-cancer group and control group

	Diameter of the main pancreatic duct		Odds ratio (95%CI)
	<2 mm	≥2 mm	
Control group (age range: 51–75 years)	6764	382	1.0
Pre-cancer group			
≥4 years before surgery	6	11	32.5 (10.9–107.3)
≥2 years before surgery	9	19	37.4 (16.0–94.3)
≥1 year before surgery	7	32	80.9 (34.7–218.2)

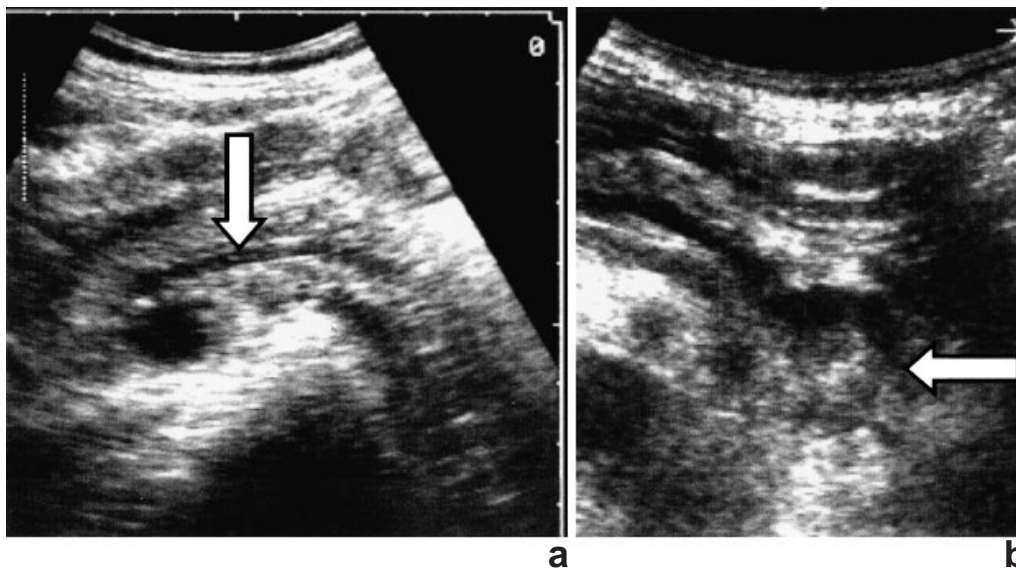


Figure 1. A case with pancreatic tail cancer. (a) In June 1990, a slight dilatation (2.5 mm) of the main pancreatic duct (arrow) was detected by sonography, but dynamic CT revealed no significant sign. In December 1991, the diameter of the main pancreatic duct had increased to 7 mm by sonography and endoscopic-retrograde pancreatography with pancreatic juice cytology was performed. However, no malignant sign was revealed except for the dilatation of the main pancreatic duct. (b) In September 1992, a round tumor 45 mm in diameter (arrow) was detected in the pancreatic tail with main pancreatic duct dilatation in the proximal part. In November 1992, pancreatic ductal adenocarcinoma in the tail of the pancreas was surgically resected by distal pancreatectomy.

51.3% of all 39 subjects at more than 1 year before surgery. When borderline dilatation (2–3 mm) was included, this finding was observed in 64.7% at more than 4 years before surgery and in 82.1% at more than 1 year before surgery. The mean diameter of the dilated main pancreatic duct also increased from 3.0 mm at more than 4 years before surgery to 3.8 mm at more than 1 year before surgery.

The cancer subsequently appeared in the distal part of the

dilated main pancreatic duct in 17 subjects (Fig. 1) and in the proximal part in 16.

The comparison between the pre-cancer and control groups is summarized in Table 3. The proportion of the dilated cases (≥2 mm) to non-dilated cases was markedly higher in the pre-cancer group than in the age-matched control group. The odds ratio was 32.5 [confidence interval (CI): 10.9–107.3] or higher.

DISCUSSION

For the screening of small pancreatic cancer, retrospective and prospective studies have been attempted using symptoms, elevation of various serum enzymes and tumor marker levels as clues (3,7–9). However, these trials managed to detect only advanced cases and the establishment of high-risk criteria was reported to be very difficult. Epidemiological studies, on the other hand, have identified cigarette smoking, a high intake of fat and/or meat, gastric cancer and peptic-ulcer surgery as risk factors for pancreatic cancer (10). However, the incidence of pancreatic cancer in such risk groups is not sufficiently high to recommend special screening. Bansal and Sonnenberg reported that pancreatitis was a risk factor for pancreatic cancer in their case-control study, although only 5.9% of pancreatic cancer cases had such a history (11).

In the present study, we retrospectively examined ultrasonograms obtained several years before the resection of the pancreatic cancer, to identify the signs of high risk. Slight dilatation of the main pancreatic duct was observed in 65% of the subjects, even more than 4 years before the resection of the pancreatic cancer, and was observed in 82% at more than 1 year before surgery. Moreover, the mean diameter of the dilated main pancreatic duct increased from 3.0 to 3.8 mm with time.

The diameter of the main pancreatic duct is generally considered to increase with age, but there has been no report on the diameter in a large population. Our findings showed the higher age group to have a higher proportion of main pancreatic duct dilatation. However, even in the 7146 control subjects in the same age range as the pre-cancer group, the proportion of the dilated cases including borderline dilatation was only 5.35%. The proportion of the dilated cases was obviously higher in the pre-cancer group subjects in whom pancreatic cancer later developed than in the control group. The odds ratio of 32.5 (95% CI: 10.9–107.3), shows the association between the main pancreatic duct dilatation and pre-cancer condition. Therefore, main pancreatic duct dilatation appears to be a sign of high risk for pancreatic cancer. In order to consider this as a case-control study, the time relation for the assessment of outcome (i.e. pancreatic cancer) and exposure (dilatation) should be comparable between cases (i.e. pre-cancer group) and controls. When comparing the exposure 4 years before the outcome, this time relation should be maintained for both cases and controls. In other words, controls should be followed and assessed as having no disease 4 years after the ultrasonographic examination. Actually, we assessed this point by using a regional cancer registry and showed that the possibility of pancreatic cancer is very low.

In the present study, the subjects were limited to those in whom ultrasonography had been performed more than 1 year before surgery. Therefore, the reason for ordering the first ultrasonographic examination may be a risk factor for pancreatic cancer. However, no particular relationship between the purpose of the first sonographic examination and subsequent pancreatic disorder was observed and none of the patients were

diagnosed as having pancreatic disease at the time of the first sonographic examination.

Concerning the mechanism of main pancreatic duct dilatation in pancreatic cancer, mechanical compression by the tumor or cancer cell invasion may cause segmental obstruction and upperstream dilatation in the main pancreatic duct. However, in our study, in 17 of 19 body or tail pancreatic cancer cases, the preceding dilatation was observed downstream of the main pancreatic duct, with the cancer subsequently appearing in the distal part. The relation between cancer in the distal part and downstream pancreatic duct dilatation remains unclear. Hyperplastic changes in the epithelium of the pancreatic duct or mucus-producing mechanisms may precede the occurrence of cancer (12) and have some role in the slight dilatation of the pancreatic duct. In addition, the pancreas with main pancreatic duct dilatation may itself be the site where pancreatic cancer originates.

Kimura et al. (13) reported two cases of microscopic ductal adenocarcinoma of the pancreas. In both cases, small cystic lesions were observed adjacent to a small cancer lesion and were presumed to be dilatations of branch ducts. Cystic lesions are more easily detected than solid lesions by sonography and are thus an appropriate target for the screening of pancreatic cancer.

The diagnostic accuracy of ultrasonography for pancreatic cancer was reported to be high (5) and ultrasonography with a real-time scanner is more advantageous than X-ray CT in the detection of cancer of the main pancreatic duct (14). Although the tail of the pancreas is sometimes difficult to observe by ultrasonography, a sitting position and having the patient consume liquids may help to improve the visualization (15,16).

Pancreatic cancer is usually detected at an advanced stage associated with peri-pancreatic infiltration and thus has a poor prognosis. To overcome this state of affairs radically, new measures are needed. The present study suggested one such potential breakthrough in detecting pancreatic cancer at a much earlier stage. Although the present study was retrospective in nature, a prospective study based on this evidence may bring beneficial results.

Therefore, in cases with main pancreatic duct dilatation, after ruling out malignancy with detailed examination, periodic checkups with non-invasive modalities such as ultrasonography are recommended. If the diameter of the pancreatic duct increases or small cysts induced by branch duct dilatation appear, a detailed examination must be performed again.

In conclusion, slight dilatation of the main pancreatic duct appears to be a risk factor for pancreatic cancer. Thus, in such subjects without pancreatic cancer, periodic checkups with a non-invasive modality are recommended for the early detection of pancreatic cancer.

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